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Neuroimmune Interactions in the Intestine

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Keywords

neuroimmune interactions, mucosal immunology, intestine, gut–brain axis, visceral pain, neuropeptides

Abstract

Recent advances have contributed to a mechanistic understanding of neuroimmune interactions in the intestine and revealed an essential role of this cross talk for gut homeostasis and modulation of inflammatory and infectious intestinal diseases. In this review, we describe the innervation of the intestine by intrinsic and extrinsic neurons and then focus on the bidirectional communication between neurons and immune cells. First, we highlight the contribution of neuronal subtypes to the development of colitis and discuss the different immune and epithelial cell types that are regulated by neurons via the release of neuropeptides and neurotransmitters. Next, we review the role of intestinal inflammation in the development of visceral hypersensitivity and summarize how inflammatory mediators induce peripheral and central sensitization of gut-innervating sensory neurons. Finally, we outline the importance of immune cells and gut microbiota for the survival and function of different neuronal populations at homeostasis and during bacterial and helminth infection.

1. INTRODUCTION

The nervous system and immune system share many similarities, as both systems monitor the environment and internal stimuli, integrating these signals to regulate homeostasis and to mediate defense responses to potential threats (1). Both systems also express receptors that recognize inflammatory mediators and pathogens (1). In response to challenges, both the nervous system and the immune system undergo adaptations and can recall memory responses to subsequent stimuli (1). Based on these similarities, it is not surprising that neuronal and immune cells harbor molecular signals and receptors that allow them to communicate with each other in a reciprocal manner (2) (**Figure 1**). Upon activation, the nervous system responds within seconds and is relatively fixed in location, whereas the immune system responds more slowly and is more motile (3). Therefore, a coordinate neuroimmune cross talk maximizes the ability of the organism to optimally regulate homeostasis and to drive a successful host defense and inflammatory response.

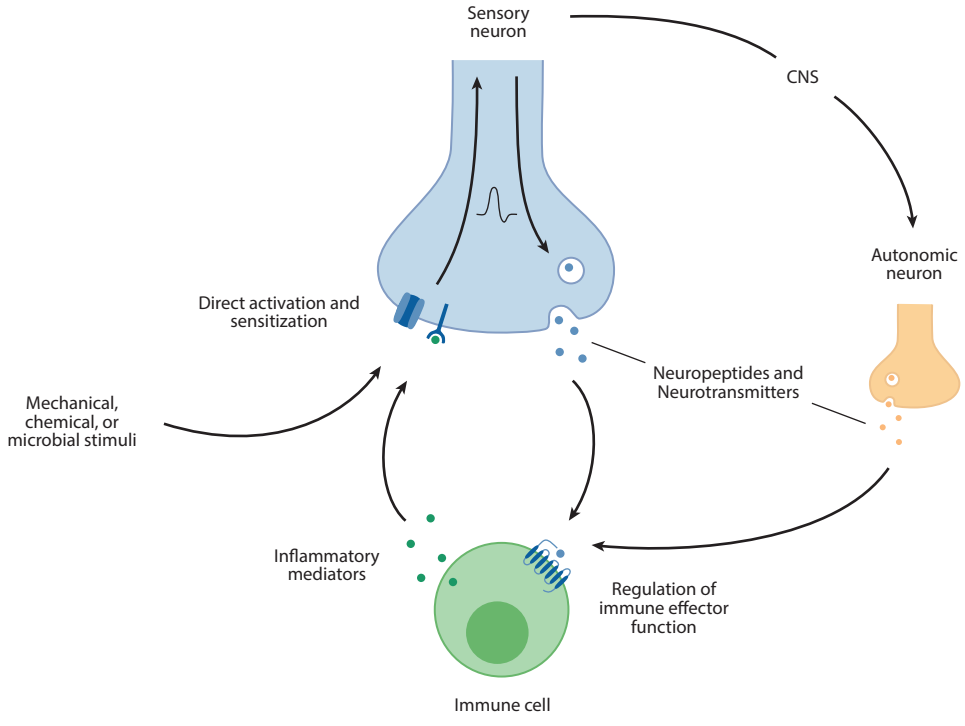

Figure 1

Neuroimmune interactions in the intestine. Immune cells are located near different neuronal populations in the intestine. Neurons communicate with immune cells either via direct mechanisms or through neural reflex circuits. Upon detection of mechanical, chemical, or microbial stimuli in the gut, sensory neurons are activated, leading to generation of action potentials that propagate to the central nervous system (CNS) to mediate visceral sensations such as pain. Sensory neurons signal to immune cells via the axon reflex, whereby action potentials back-propagate along neighboring nerve branches toward the nerve terminals, which causes neuropeptide release that can signal to immune cells. Immune cells release inflammatory mediators, such as cytokines, lipid mediators, and proteases, during inflammation or infection, which can also directly activate sensory neurons or sensitize them, thereby lowering their activation threshold. Signals from the gut also induce neural reflex circuits via the brainstem and spinal cord to parasympathetic or sympathetic neurons of the autonomic nervous system that signal to the gut via neurotransmitters that act on immune cells. Locally within the gut, enteric neurons release neuropeptides and neurotransmitters that bind to receptors expressed on immune cells and regulate their effector function.

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An involvement of neurons in inflammatory processes had already been described 2,000 years ago by Cornelius Celsus with his observation that *dolor* (pain) is one of the four cardinal signs of inflammation (4, 5). In the early twentieth century, several scientists used denervation and electrical stimulation to show that peripheral neurons can directly drive vasodilation and inflammatory processes, a process that was termed neurogenic inflammation (6). This process starts with the activation of sensory neurons, which generate action potentials that not only travel toward the central nervous system (CNS) in an afferent direction but also propagate at branch points antidromically back to nerve terminals (7, 8). At peripheral nerve terminals, action potentials initiate calcium-dependent release of neuropeptides from dense core vesicles into the tissue environment (7, 9). These neuropeptides include substance P and calcitonin gene-related peptide (CGRP), which promote vascular permeability and vasodilation, respectively (10). Further research showed that these neuropeptides can regulate the function of immune cells, which either ameliorates or worsens inflammatory and infectious diseases (2, 8). Conversely, immune cells also potently regulate the function of neurons, which express receptors for immune-derived factors such as cytokines, proteases, and lipid mediators (11). For example, immune mediators lower the threshold of nociceptor sensory neurons, leading to peripheral sensitization to noxious stimuli and pain hypersensitivity (12).

The nervous and immune systems are highly diverse, with intricate cellular networks in tissues. Recently, we have started to gain a much better understanding of the exact cellular and molecular mechanisms of neuroimmune interactions owing to technical and genetic advances in single-cell RNA-sequencing (scRNA-seq), intravital multiphoton microscopy, tissue-clearing techniques, genetic calcium indicators, and optogenetic and chemogenetic approaches (1, 13). In particular, the gastrointestinal tract is a highly specialized and complex organ that is in close contact with the environment, balancing nutrient uptake, digestion, and motility with the ability to mediate host defense (14). The gastrointestinal tract is densely innervated by the nervous system, housing millions of neurons and receiving input from the brain and spinal cord (15). It is also populated by numerous innate and adaptive immune cells, which are essential for mediating tolerance to food antigens and mounting defense responses to invading pathogens (14, 16). The intestine not only receives input from the brain but also communicates with the brain, a bidirectional pathway termed the gut–brain axis (17). The effector function of immune and nonimmune cells in the brain is regulated by bacterial metabolites in the intestine, and immune cells migrate from the intestine to the brain in a disease context (17). Therefore, the focus of this review is the bidirectional neuroimmune cross talk in the intestine, since interactions between neurons and gut-resident immune cells have important implications for homeostasis and intestinal inflammation.

Neuropeptide: a small peptide that is produced and released by neurons

Nociceptor: sensory neurons that are activated by noxious stimuli and induce the sensation of pain

Ganglia: aggregation of neuronal cell bodies

2. INTESTINAL ANATOMY AND INNERVATION

The intestine consists of the small and large intestine, which are composed of different layers, including the epithelium, lamina propria, submucosa, and muscle layer (16) (**Figure 2*a***). The intestinal layers are innervated by different types of neurons, which can be classified as gut-intrinsic or gut-extrinsic neurons (18). While the cell bodies of intrinsic neurons are located within the intestinal wall, the cell bodies of extrinsic neurons are located outside of the gut in sensory or autonomic ganglia and brainstem, sending projections to the gastrointestinal tract (18). Intrinsic and extrinsic intestinal neurons in the mouse have been characterized in the past on the basis of morphology, electrophysiological recordings, and immunohistochemical methods (19–24) and more recently with the advent of RNA-sequencing based on transcriptional expression profiles. These neurons constitute both sensory and autonomic branches of the peripheral nervous system (2).

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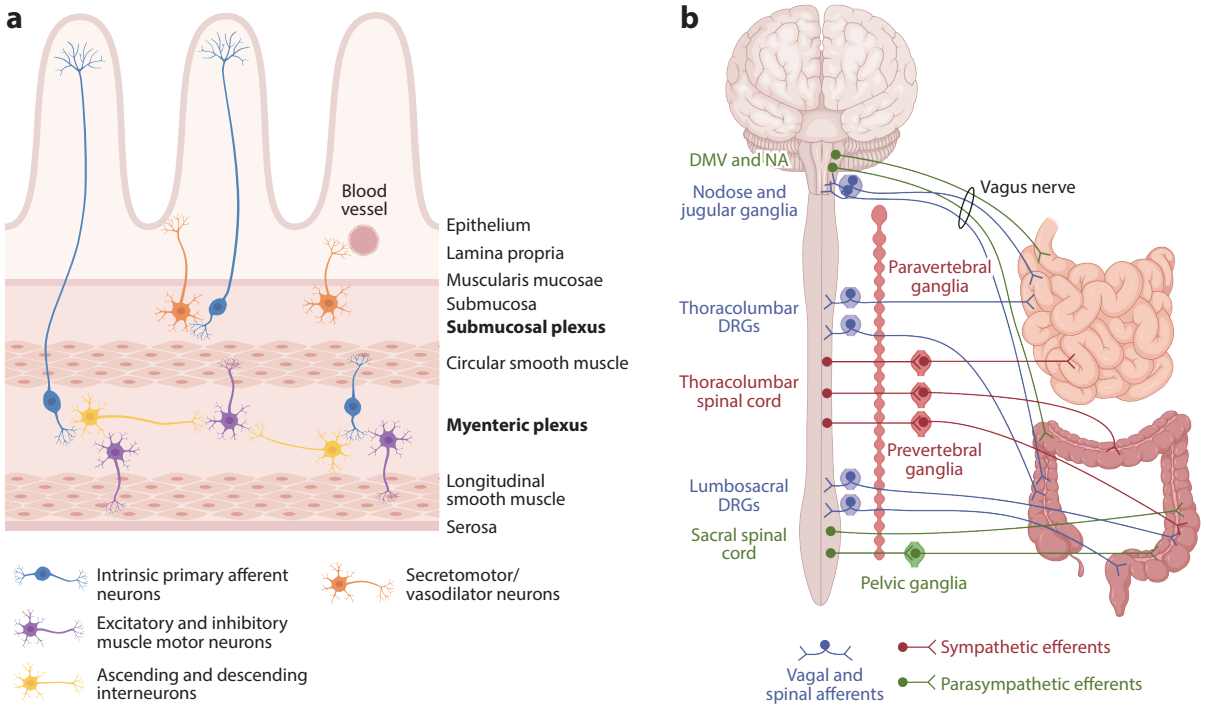

Figure 2

Intrinsic and extrinsic innervation of the intestine. (*a*) Anatomy of the enteric nervous system. The layers of the intestine consist of the epithelium, followed by the lamina propria, muscularis mucosae, and submucosa. Adjacent lies the muscularis, consisting of an inner circular and outer longitudinal smooth muscle layer, and serosa. Enteric neurons reside in the submucosal plexus, located within the submucosa, and the myenteric plexus, between the circular and longitudinal smooth muscle layers. The myenteric plexus houses intrinsic primary afferent neurons (IPANs), interneurons, and excitatory and inhibitory muscle motor neurons that innervate the muscle layers to coordinate intestinal motility. The submucosal plexus houses IPANs and secretomotor/vasodilator neurons that innervate the mucosa, where they regulate secretion and vasodilation. (*b*) Extrinsic innervation of the intestine. The gut is also innervated by multiple types of extrinsic sensory and motor neurons, whose cell bodies reside outside the gut. Vagal sensory afferents (*purple*) have cell bodies located in nodose and jugular ganglia and project via the vagus nerve to the small intestine and proximal colon. Spinal sensory afferents (*purple*) have cell bodies in the dorsal root ganglia (DRGs) and project to the small intestine and colon or to the distal colon and rectum. Sympathetic efferents (*red*) arise in the thoracolumbar spinal cord and project to paravertebral and prevertebral ganglia, where they synapse onto neurons that innervate the small intestine and colon. Parasympathetic efferents (*green*) arise in the dorsal motor nucleus of the vagus (DMV) and nucleus ambiguous (NA) or the sacral spinal cord. DMV and NA neurons innervate the small intestine and proximal colon via the vagus nerve, and sacral spinal cord neurons innervate the colon. Panel *b* adapted from images created with BioRender.com.

2.1. Intrinsic Neurons

Intrinsic neurons, whose cell bodies are fully contained within the gastrointestinal tract, form the enteric nervous system (ENS), which functions to mediate sensory, peristaltic, and secretory function independently of the CNS (15, 18). The ENS consists of two plexuses, which comprise enteric ganglia containing neuronal cell bodies and networks of neuronal processes (15, 25, 26) (**Figure 2*a***). The myenteric plexus, also termed Auerbach's plexus, is dispersed between the circular and longitudinal smooth muscles of the muscle layer (18, 27) and is involved predominantly in the regulation of intestinal motility (28). The submucosal plexus, also termed Meissner's plexus, is positioned within the submucosa (18, 27) and regulates nutrient uptake and secretion (28).

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Enteric neurons consist of different neuronal types, including (*a*) intrinsic primary afferent neurons (IPANs), which are sensory neurons that can be activated directly by mechanical stretch or indirectly via serotonin (5-HT) produced by enterochromaffin cells; (*b*) ascending and descending interneurons; and (*c*) excitatory and inhibitory motor neurons that innervate smooth muscles (15, 27). These three types of neurons form the peristaltic reflex circuit of the ENS, which mediates sensing of distension of the intestinal wall and promotes forward propulsion of food (15, 27). Another subset of enteric neurons that are less well studied are intestinofugal neurons, which have axonal projections outside of the intestine (15, 29) and respond directly to mechanical stimuli or are activated by other enteric neurons (28, 29).

Cholinergic: describes neurons that express the neurotransmitter acetylcholine

While the function of these neuronal subtypes is broadly defined, the molecular identities and specific subtypes that mediate these functions are still being elucidated. scRNA-seq of nuclei from the mouse ENS has revealed 12 neuron subsets in the ileum and 21 neuron subsets in the colon of adult mice (30). The neurons in the colon expressed *Nos1* (nitrergic), *Chat* (cholinergic), or both and were further categorized as putative sensory neurons (*Calcb*$^{+}$ *Calca*$^{+/-}$), interneurons (*Penk*$^{+}$), excitatory motor neurons (*Chat*$^{+}$ *Tac1*$^{+}$), inhibitory motor neurons (*Nos1*$^{+}$), or secretomotor/vasodilator neurons (*Glp2r*$^{+}$) (30). While this study analyzed enteric neurons from all intestinal layers (30), other studies analyzed enteric neurons specifically from the mouse myenteric plexus by population-based RNA-seq (31) and scRNA-seq or single-nucleus RNA-seq (13, 32–34). Transcriptional analysis revealed that transcriptional profiles of enteric neurons are specific to the location within the gastrointestinal tract and that their gene expression is also modulated by the microbiota (31, 35). In addition to these studies of the mouse ENS, the human ENS was also analyzed transcriptionally by molecular profiling (30, 33, 34). Despite these recent advances in the transcriptional characterization of enteric neurons, it remains to be determined how each of these distinct neuronal cell types regulates different intestinal processes and cross talks with the immune system.

2.2. Extrinsic Neurons

Extrinsic neurons connect the gut to the brain and spinal cord and can be further divided into extrinsic sensory afferent neurons, which transmit sensory information to the CNS, and sympathetic and parasympathetic neurons, which innervate and modulate cell types in the gut as well as in the ENS (18, 36).

2.2.1. Extrinsic sensory afferent neurons. The intestine is innervated by extrinsic sensory afferent neurons, which transmit sensory information from the intestine to the spinal cord and brain (29, 37) (**Figure 2*b***). Extrinsic sensory afferent neurons are pseudounipolar neurons, whose peripheral axon innervates the intestine and whose central axon projects to the brainstem or spinal cord (18, 38–40). Depending on the location of the cell bodies within the different ganglia, extrinsic sensory afferent neurons can be further divided: Vagal afferent neurons are located in nodose and jugular ganglia, with central projections to the brainstem and peripheral axons projecting via the vagus nerve to the small intestine and proximal colon (29, 41). The small intestine and proximal colon are also innervated by thoracolumbar spinal afferent neurons, whose cell bodies are located in the thoracolumbar dorsal root ganglia (DRGs) and innervate the small intestine and colon via the splanchnic nerves (29, 42). Thoracolumbar spinal afferent neurons also innervate the lower colon and rectum, which receive additional innervation via pelvic and rectal nerves from lumbosacral spinal afferent neurons (29, 42–44). Based on their terminal morphology and location of innervation, sensory afferents can be classified as intraganglionic laminar afferents, mucosal afferents, muscular-mucosal afferents, intramuscular afferents, or vascular afferents (29, 43). These sensory subtypes can respond to different stimuli, including mechanical stretch,

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hormones, and chemical irritants (29, 43). Silent afferents are also thought to exist that at homeostasis are unresponsive to mechanical stimuli but can become responsive during inflammation (29, 43).

Vagal and DRG sensory neurons are highly diverse at a molecular level. Almost a decade ago, bulk transcriptional analysis started revealing subpopulations of sensory neurons (45–48). Several groups then performed scRNA-seq of vagal ganglia (49) and DRGs from mice (13, 50–52) and DRGs from nonhuman primates (53), identifying up to 24 neuronal clusters in vagal ganglia and 17 different neuronal clusters in DRGs. While these studies provide an unbiased characterization of neuronal subtypes present in DRGs, it was unclear which specific molecular subtypes innervate the intestine. This drawback was addressed by Hockley and colleagues (54), who specifically targeted sensory neurons innervating the mouse colon by labeling them retrogradely with a fluorescent dye and subsequently isolating them from thoracolumbar and lumbosacral DRGs. scRNA-seq identified seven neuronal clusters, including peptidergic, nonpeptidergic, and neurofilament-containing subtypes (54). Of these gut-innervating neuronal clusters, five were found in both thoracolumbar and lumbosacral DRGs, whereas two clusters were specific for lumbosacral DRGs (54), suggesting functional differences. Peptidergic subtypes express the neuropeptide CGRP, encoded by *Calca*, and substance P, encoded by *Tac1* (54). These subtypes also express transient receptor potential cation channel subfamily V member 1 (TRPV1), which is activated by heat, capsaicin, and protons (54–56). The ion channel TRPA1 is expressed by peptidergic subsets observed in both thoracolumbar and lumbosacral DRGs and senses inflammatory products and specific chemicals (54–56). The voltage-gated sodium channel $Na_v1.8$, encoded by *Scn10a*, is expressed by different neuronal subtypes and is involved in the generation of action potentials (54, 55). DRG sensory neurons also express different Toll-like receptors (TLRs), including TLR4 and TLR5, and can directly respond to microbes and their products, including lipopolysaccharide (LPS), an outer wall glycolipid from gram-negative bacteria (57–60).

Preganglionic neuron: neurons located in the spinal cord whose axons synapse onto postganglionic neurons

Paravertebral ganglia: sympathetic ganglia that form a chain and are located next to the vertebral column

Prevertebral ganglia: sympathetic ganglia that are localized in front of the vertebral column

Noradrenergic: describes neurons that express the neurotransmitter noradrenaline

Postganglionic neuron: neurons located in ganglia that innervate the target organ

2.2.2. Extrinsic sympathetic efferent neurons. The sympathetic pathway consists of a two-neuron relay, with a cholinergic preganglionic neuron, which is located in the thoracolumbar spinal cord, that projects to paravertebral ganglia and prevertebral ganglia, where it synapses with noradrenergic postganglionic neurons, which then project to peripheral tissues, including the gut (26, 61, 62) (**Figure 2*b***). Postganglionic neurons of the paravertebral ganglia innervate blood vessels in the intestine and induce vasoconstriction (63). Postganglionic neurons of the prevertebral ganglia have a similar function but also innervate other targets, such as neurons in the myenteric and submucosal ganglia to inhibit motility and secretion, as well as Peyer's patches and mucosa (63, 64).

2.2.3. Extrinsic parasympathetic efferent neurons. The parasympathetic pathway consists of a cholinergic preganglionic neuron that synapses with cholinergic postganglionic neurons (65) (**Figure 2*b***). Parasympathetic preganglionic neurons located in the dorsal motor nucleus of the vagus and the nucleus ambiguous project via the vagus nerve to the myenteric plexus in the gut, where they synapse with enteric neurons located in the proximal small intestine and proximal colon (18, 26, 62). In contrast, parasympathetic preganglionic neurons located in the sacral spinal cord directly innervate the distal colon or project to pelvic ganglia, where they synapse onto postganglionic neurons that innervate the distal colon via rectal nerves (18, 62).

3. REGULATION OF IMMUNE CELLS BY NEURONS

Although it has been known since the last century that nociceptor sensory neurons can induce neurogenic inflammation (6), the extent to which neuroimmune interactions regulate tissue inflammation and host defenses has long been underappreciated. Recent studies revealed that

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besides sensory neurons, other neuronal populations also communicate with immune cells in the intestine and modulate intestinal inflammation. While several studies focused initially on the role of neurons in colitis, more recently the field moved toward a characterization of the signaling pathways that are used by neurons to regulate the function of particular immune cells. Therefore, in this section we first summarize the contribution of extrinsic and intrinsic neurons to the development of colitis and then review the molecular mechanisms by which neurons signal to different intestinal immune cells.

3.1. Role of Different Neuronal Populations in Colitis

Inflammatory bowel diseases (IBDs) are defined by chronic relapsing intestinal inflammation and encompass ulcerative colitis and Crohn's disease (66). Whereas the mucosa and submucosa of the colon are inflamed in ulcerative colitis, all layers of the intestinal wall of the distal ileum and colon are inflamed in Crohn's disease (66). IBD is also characterized by pain and stress, which are mediated by the nervous system (43, 67–69). Increasing evidence shows that the nervous system also plays a role in regulating the outcome of colitis.

Neuroimmune regulation and a signaling pathway between the brain and periphery that regulates inflammatory responses were discovered over two decades ago and termed the cholinergic anti-inflammatory pathway (11). Electrical stimulation of the vagus nerve reduced serum tumor necrosis factor (TNF) levels and endotoxic shock in response to a lethal dose of LPS (70). Further experiments revealed that the vagus nerve signals to the splenic nerve, which induces acetylcholine production by T cells in the spleen. Acetylcholine then negatively regulates TNF production by splenic macrophages in a nicotinic acetylcholine receptor α7 subunit–dependent manner (71–74). This anti-inflammatory pathway has a protective effect not only in LPS-induced endotoxic shock but also in colitis. Vagus nerve stimulation decreased disease severity in models of trinitrobenzene sulfonic acid (TNBS)- or dextran sulfate sodium (DSS)-induced colitis (75–77) and increased the survival rate in a model of oxazolone-induced colitis (78). Similarly, stimulation of cholinergic signaling pathways decreased disease severity of DSS-induced colitis (79). In contrast, vagotomy increased severity of DSS-induced colitis and colonic IL-6 and TNF-α levels (80, 81).

Similar to the anti-inflammatory pathway, sympathetic neuron activation could ameliorate colitis. Daily optogenetic activation of sympathetic neurons during DSS-induced colitis reduced body weight loss and intestinal inflammation in a noradrenaline-dependent manner (82). In contrast, systemic administration of noradrenaline resulted in increased body weight loss and inflammation, suggesting that local versus systemic release of noradrenaline may determine the effect (82). This detrimental effect of systemic noradrenaline on DSS-induced colitis has also been reported by another group that activated the α_2-adrenoceptor during colitis by systemic administration of an agonist (83). Further experiments revealed that optogenetic activation of sympathetic neurons decreased expression of the cell adhesion molecule MAdCAM-1 on endothelial cells (82). MAdCAM-1 is important for lymphocyte extravasation during inflammation, suggesting that sympathetic neurons negatively regulate immune cell infiltration, which ameliorates intestinal inflammation (82).

Besides the parasympathetic and sympathetic pathways, nociceptors play a protective role against DSS-induced colitis in mice (84, 85). Chemical ablation of $TRPV1^+$ neurons or chemogenetic silencing of nociceptive neurons using designer receptors exclusively activated by designer drugs (DREADDs) resulted in increased body weight loss and disease severity and worse intestinal inflammation during DSS-induced colitis compared with control mice (84, 85). In contrast, chemogenetic activation of nociceptive neurons was protective during DSS-induced colitis (84, 85). In the absence of sensory neurons, the neuropeptides substance P and CGRP were reduced and microbial dysbiosis was observed, suggesting that nociceptors exert their protective effect via

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these neuropeptides and the microbiota (84, 85). Substance P–deficient mice showed increased susceptibility to DSS-induced colitis, which could be transferred into germ-free mice by microbial transfer, suggesting that substance P ameliorates intestinal inflammation by influencing the microbial composition (84). However, in a different model of colitis induced by the chemical oxazolone, substance P plays a proinflammatory role, as substance P–deficient mice developed less severe oxazolone-induced colitis compared with wild-type mice (86). In contrast, CGRP shows an anti-inflammatory effect in this model of colitis, as the histological disease score was higher in CGRP-deficient mice than in wild-type mice (86). In addition to substance P and CGRP, the neuropeptide vasoactive intestinal peptide (VIP), which is expressed in both vagal sensory neuron and enteric neuron subsets (30, 49), seems to play a role in colitis, although the effect varies between studies. Whereas one research group showed that VIP ameliorates disease severity during TNBS-induced colitis (87, 88), another group did not observe any protective effect of VIP (89). Moreover, germline deletion of VIP resulted in slightly reduced body weight loss and decreased levels of IL-6 and TNF-α in TNBS-induced colitis, indicating a proinflammatory role of endogenous VIP (90).

Neurotransmitter: a small molecule released by neurons at the synapse to transmit information

A recent study by Koren et al. (91) suggests that the nervous system may induce memory of inflammatory challenge in the gut and recalls information related to these previous immune responses with subsequent challenge in the context of DSS-induced colitis. The authors injected a neuron-specific viral vector encoding a Cre-dependent fluorophore into the brain of $Fos^{2A\text{-}iCreERT2}$ mice to label activated neurons at a specific anatomical location upon tamoxifen treatment. This viral vector also expressed a stimulatory DREADD, which allows reactivation of neurons with the chemical ligand clozapine *N*-oxide. Using these genetic and viral approaches, the authors showed that reactivation of neurons in the insular cortex that had been active during previous DSS-induced colitis induces intestinal inflammation partially similar to the inflammatory response observed during colitis. In contrast, unspecific inhibition of neurons in the insular cortex during colitis using a viral vector expressing an inhibitory DREADD ameliorated some signs of inflammation (91).

3.2. Effect of Neurons on Immune Cells

Neurons regulate not only colitis but also other intestinal diseases and enteric infections by modulating the function of immune cells (**Figure 3**). The intestine contains many different immune cells that are located within different areas, such as intraepithelial lymphocytes in the epithelium and innate lymphoid cells (ILCs), eosinophils, mast cells, macrophages, dendritic cells (DCs), T cells, and IgA-producing plasma cells in the lamina propria (16). Immune cells express cognate receptors for neurotransmitters and neuropeptides, allowing them to respond to mediators produced by different neuronal subtypes (92). We discuss recent findings that show how neurons regulate the function of different immune cells.

3.2.1. Neuron–ILC interactions. ILCs are resident innate immune cells present in different tissues, including the intestine (94). On the basis of their effector function and developmental pathway, ILCs can be subdivided into natural killer cells, ILC1s, ILC2s, ILC3s, and lymphoid tissue–inducer cells (94, 95). Despite their functional similarities to T cells, ILCs do not express rearranged antigen receptors but instead respond to cytokines and inflammatory mediators (96). ILC2s promote defense against helminths but also contribute to the development of allergies, whereas ILC3s are important for intestinal homeostasis and defense against extracellular bacteria and fungi (94, 95).

The neuropeptide neuromedin U (NMU) is expressed by cholinergic neurons in the intestine (97). The type 2 alarmin cytokine IL-33 or helminth *Nippostrongylus brasiliensis* products

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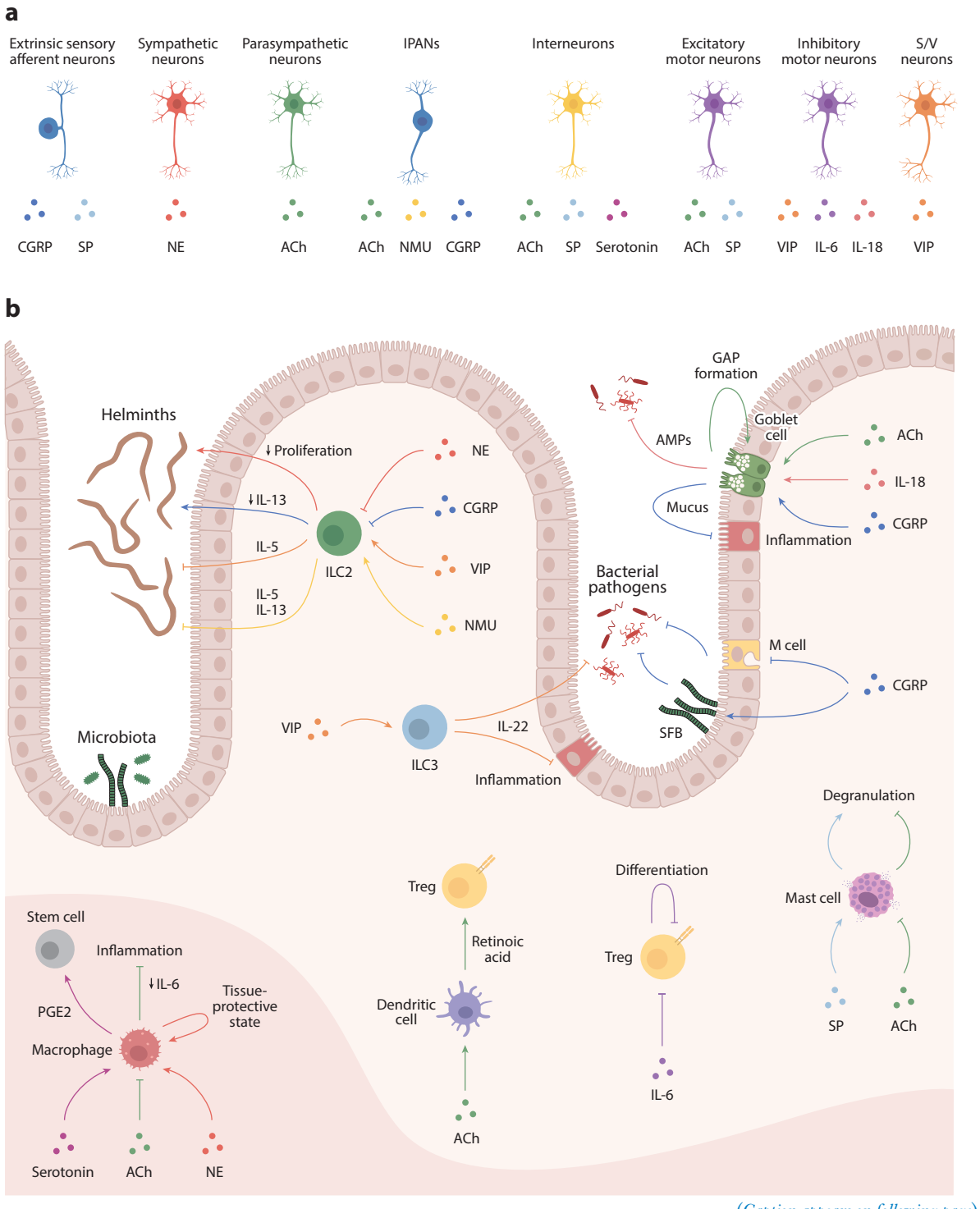

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Figure 3 (*Figure appears on preceding page*)

Neuronal regulation of immune cell effector function. (*a*) Neuropeptides and neurotransmitters are produced by different gut-innervating neuronal populations, which signal to both neuronal and immune cells. Peptidergic subtypes of dorsal root ganglia sensory neurons express calcitonin gene-related peptide (CGRP) and substance P (SP) (13, 54). Postganglionic sympathetic neurons express norepinephrine (NE) and postganglionic parasympathetic neurons express acetylcholine (ACh). Within the enteric nervous system, a subset of intrinsic primary afferent neurons (IPANs) express choline acetyltransferase (ChAT), which mediates synthesis of ACh, neuromedin U (NMU), and CGRP (30, 32). Subsets of enteric interneurons express ChAT, SP (30), or serotonin (32). Excitatory motor neurons express ChAT and SP, whereas inhibitory motor neurons express vasoactive intestinal peptide (VIP) and IL-6 (30, 32, 93). A subset of secretomotor/vasodilator (S/V) neurons express VIP (30). IL-6 and IL-18 are expressed by different subtypes of enteric neurons (13). (*b*) The effector function of different intestinal immune cell populations is regulated by neuronal mediators, including neuropeptides, neurotransmitters, and cytokines. Both NMU and VIP promote type 2 innate lymphoid cell (ILC2) cytokine production, which facilitates helminth expulsion. In contrast, CGRP negatively regulates IL-13 expression and NE inhibits proliferation, leading to a diminished antihelminth response. VIP promotes IL-22 production by type 3 innate lymphoid cells (ILC3s), which reduces bacterial infection and intestinal inflammation. NE induces tissue-protective macrophages, whereas ACh negatively regulates macrophage production of IL-6, which inhibits intestinal inflammation. Serotonin induces the release of prostaglandin E2 (PGE2) from macrophages, which promotes stem cell renewal. ACh also promotes retinoic acid production by dendritic cells, which supports T regulatory cell (Treg) generation. The differentiation of Tregs is inhibited by neuronal production of IL-6. Mast cells are regulated by substance P, which can promote degranulation, and ACh, which inhibits degranulation. Neuropeptides and neurotransmitters also regulate epithelial cell function. CGRP reduces M cell density and supports segmented filamentous bacteria (SFB), which protect against bacterial infection. CGRP also promotes goblet cell mucus release, which limits intestinal inflammation during colitis. IL-18 produced by enteric neurons promotes the production of antimicrobial proteins (AMPs) by goblet cells, thereby limiting bacterial infection, and ACh induces the formation of goblet cell–associated antigen passages (GAPs).

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promote NMU expression in neuronal organoid cultures in an MYD88-dependent manner (98), suggesting that cholinergic neurons can sense the presence of helminths via TLRs. ILC2s are in close proximity to cholinergic neurons (97), and the receptor for NMU, neuromedin U receptor 1 (Nmur1), is found exclusively on ILC2s (97–99), indicating a potential interaction. Indeed, upon stimulation with NMU, intestinal ILC2s proliferate and express increased levels of type 2 cytokines in an Nmur1-dependent manner (97, 98). In a model of *N. brasiliensis* infection, recombinant NMU promotes eosinophilia and helminth expulsion (97, 98). Adoptive transfer of wild-type versus Nmur1-deficient ILC2s into *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice confirmed the important role of Nmur1-expressing ILC2s in mounting a type 2 immune response against helminths (97, 98). This neuroimmune interaction seems to be conserved between tissues, since NMU, in particular in combination with IL-25, has a similar proinflammatory effect on lung ILC2s that results in exacerbated airway inflammation (97, 99).

Another neuropeptide that activates ILC2s is VIP, which is expressed in the intestine by enteric neurons that do not express substance P or tyrosine hydroxylase (100, 101). The receptors for VIP, Vipr1 and Vipr2, are expressed by intestinal ILC2s and signaling via Vipr2 promotes IL-5 production by ILC2s in vitro (102). Since VIP is upregulated after food intake (101, 103) and IL-5 induces eosinophilia, this neuroimmune pathway may be important in promoting eosinophil recruitment after nutrient intake (102). Another study showed that VIP synergizes with IL-33 to promote IL-5 production by ILC2s (103). In a model of helminth infection with *Trichuris muris*, VIP signaling in ILC2s is important for potentiating ILC2 responses and helminth expulsion (103). This signaling pathway could potentially also promote an allergic immune response in the intestine, since in the lung VIP has been shown to contribute to the development of allergic airway inflammation by promoting type 2 cytokine production by ILC2s and Th2 cells (104).

In contrast to NMU and VIP, other neuropeptides and neurotransmitters can have an inhibitory effect on ILC2s. CGRP is expressed in the small intestine by choline acetyltransferase (ChAT)$^{+}$ enteric neurons (105). ILC2s are in close contact with these neurons and express the receptor for CGRP, which consists of a coreceptor complex formed by Ramp1 and Calcrl (105). Short-term cultures revealed a differential effect of CGRP on activated intestinal ILC2s: Whereas

CGRP increased IL-5 expression, it inhibited IL-13 expression and proliferation (105). These results suggest a detrimental role of CGRP in helminth infection, as it inhibits IL-13 expression important for mucus production and helminth expulsion (94). Indeed, adoptive transfer of wild-type or Ramp1-deficient bone marrow into *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice revealed a decreased worm burden in the absence of Ramp1 signaling (106). In a model of ovalbumin (OVA)-induced food allergy, recombinant CGRP also inhibits ILC2 expansion (105). This neuroimmune pathway is also observed in the lung, where it reduces the severity of IL-33-induced airway inflammation in the absence of adaptive immune cells (106, 107).

Another negative regulator of ILC2 responses is norepinephrine expressed by adrenergic neurons in the small intestine (108). ILC2s are neighboring adrenergic neurons and among other immune cells express the norepinephrine receptor, β_2-adrenergic receptor (108). In a model of *N. brasiliensis* infection, signaling via the β_2-adrenergic receptor inhibits ILC2 expansion, resulting in increased worm burden (108). A similar inhibitory effect is observed in the lung during airway inflammation, suggesting a conserved neuroimmune pathway (108).

In addition to ILC2s, ILC3s are regulated by neuropeptides. Similar to ILC2s, ILC3s are located next to VIP$^+$ neurons in the intestine and express *Vipr2*, one of the receptors for VIP (100, 101, 103). Stimulation of intestinal ILC3s with VIP induces IL-22 production, and this effect is potentiated when given in combination with IL-23 (101, 103). Since IL-22 is important for epithelial barrier function (109), the VIP–ILC3–IL-22 axis might play an important role in intestinal inflammation and infection. Indeed, in a DSS-induced colitis model, *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice with adoptively transferred Vipr2-deficient ILC3s develop stronger intestinal inflammation compared with *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice with wild-type ILC3s (101). Similarly, in a model of bacterial infection with *Citrobacter rodentium*, the bacterial burden is increased in mice with a conditional deletion of Vipr2 in ILC3s (Rorγt-Cre$^+$ Vipr2$^{fl/fl}$) compared with controls (103). While the aforementioned studies observe an increase in IL-22 production in ILC3s upon VIP stimulation, a study by Talbot et al. (100) reports the contrary effect. The authors show that chemogenetic activation of VIP$^+$ neurons increases susceptibility to *C. rodentium* infection and that inhibition of neurons decreases bacterial load (100). Their data support that signaling via Vipr2 negatively regulates IL-22 production by CCR6$^+$ ILC3s, which results in a decreased expression of antimicrobial peptides (100). Using mice with a Rorγt$^+$ cell–specific deletion of Vipr2, Talbot et al. (100) found decreased length of segmented filamentous bacteria and diminished uptake of lipids. The difference in outcome between these studies could be due to different experimental approaches and timing of experiments, as well as the microbiota. In addition to the coordination of intestinal responses to food intake, VIP is also associated with circadian rhythms (110). Cytokine expression of intestinal ILC3s follows circadian oscillations, which are regulated by the light–dark cycle as well as brain-derived signals (111–113). Expression of Arntl, a key regulator of the circadian rhythm, is important for ILC3 homeostasis (112, 113) and defense against bacterial infection (113).

Notably, recent research has revealed that neuropeptides and neurotransmitters are expressed not only by neurons but also by ILC2s and ILC3s themselves. CGRP is expressed by intestinal and lung ILC2s, which upregulate its expression during intestinal inflammation and helminth infection, suggesting a negative-feedback circuit to suppress ILC2 responses during tissue inflammation (105–107). ChAT, an enzyme involved in the synthesis of acetylcholine, is expressed by lung and intestinal ILC2s during helminth infection, and conditional deletion in IL-7R$^+$ cells or Rorα$^+$ cells results in reduced ILC2 numbers and decreased worm expulsion, suggesting that ILC2-derived acetylcholine contributes to antihelminth responses (114, 115). Similarly, tryptophan hydroxylase 1 (Tph1), the enzyme involved in serotonin synthesis, is also expressed in intestinal ILC2s, and lymphocyte-specific deletion of Tph1 results in diminished inflammatory ILC2 responses and impaired helminth expulsion (116). These studies show that immune cells

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can develop neuron-like characteristics and that this could lead to functional impacts on their phenotype.

3.2.2. Neuron–mast cell interactions. Mast cells play important roles in helminth infection by promoting a type 2 immune response (117) and in allergies by releasing preformed mediators, such as histamine, that induce vasodilation, vascular permeability, and bronchoconstriction (118). Two subsets of mast cells exist in mice: connective-tissue mast cells, which are located in the muscularis propria, and mucosal mast cells (MMCs), which are located in the mucosa (119).

MMCs are observed near $CGRP^+$ cholinergic nerves in the colon of mice with food allergy (120) and near peptidergic neurons in the intestines of helminth-infected rats (121). Similarly, mast cells also neighbor nerves in colons from patients with irritable bowel syndrome (IBS) (122). Substance P and CGRP induce degranulation of rodent MMCs (123, 124), whereas substance P and VIP promote degranulation of primary cultured human mast cells (125). While these results suggest that mast cell degranulation is regulated by neuropeptides, another study reports that unpurified mast cells isolated from human intestines do not degranulate in response to substance P, VIP, or CGRP (126). However, upregulation of NK-1, the receptor for substance P, was observed upon IgE receptor cross-linking in this study (126).

The neurotransmitter acetylcholine also presumably negatively regulates mast cells. Mucosal-type murine bone marrow–derived mast cells express the α7 nicotinic acetylcholine receptor (nAChR) subunit and a specific agonist for this subunit reduced the degranulation induced by IgE-mediated activation (127). In a model of OVA-induced food allergy, administration of an nAChR agonist reduced colonic MMC numbers and development of allergic diarrhea (120). Another study reports that vagus nerve stimulation during OVA-induced food allergy reduced intestinal mast cell numbers and mMCP-1 levels; however, this effect did not depend on α7 nAChR signaling (128). Myenteric neurons can also activate mucosal-type bone marrow–derived mast cells based on coculture experiments, which was partly dependent on adenosine A3 receptor signaling in mast cells (129).

3.2.3. Neuron–macrophage interactions. Intestinal macrophages can be classified as lamina propria macrophages or muscularis macrophages depending on their molecular profiles as well as their location within the tissue (130). Lamina propria macrophages are located close to the intestinal epithelium and are important for the clearance of dead cells and pathogens, transfer of luminal antigens, and regulation of intestinal ILC and T cell responses (130, 131). In contrast, muscularis macrophages are located in the muscle layers of the intestine and play an important role in intestinal homeostasis and colonic motility (130).

Enteric neurons provide crucial support for muscularis macrophages in the intestine. Muscularis macrophages are located near enteric neurons and express *Csf1r*, the receptor for colony-stimulating factor 1 (CSF1) (132). Enteric neurons produce the ligand CSF1, which is an essential growth factor for the development of muscularis macrophages (132). Sympathetic neurons protect the tissue and enteric neurons by regulating muscularis macrophages during bacterial infection. In response to bacterial infection with *Salmonella enterica* serovar Typhimurium mutant *spiB*, extrinsic sympathetic neurons produce norepinephrine, which stimulates β_2 adrenergic receptors on muscularis macrophages to promote a tissue-protective cell state (133). Moreover, β_2 adrenergic signaling in muscularis macrophages promotes arginase 1–mediated production of polyamines, which reduces death of enteric neurons after enteric bacterial infection (134).

Parasympathetic pathways are also involved in intestinal inflammation. Macrophages are located next to cholinergic nerves in the myenteric plexus (135) and express α7 nAChR (136). Anterograde tracing of vagal efferents innervating the intestine revealed that macrophages are

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not in close proximity to cholinergic vagal efferents but rather are close to cholinergic myenteric neurons, suggesting that muscularis macrophages are regulated by acetylcholine released by enteric neurons (136). Indeed, stimulation of LPS-activated peritoneal macrophages with nicotine decreased the secretion of TNF and IL-6 in vitro (135). In a model of surgery-induced intestinal inflammation, vagus nerve stimulation negatively regulated peritoneal IL-6 levels and intestinal inflammation (135). This inhibitory effect was independent of splenic innervation and T cells, suggesting that the vagus nerve innervates cholinergic enteric neurons, which upon release of acetylcholine inhibit IL-6 release by muscularis macrophages (136). In a model of OVA-induced food allergy, vagus nerve stimulation promoted the uptake of OVA by CX3CR1^{hi} macrophages, suggesting that the vagus nerve also regulates antigen uptake in different immune cell populations (128).

Enteric serotonergic neurons also regulate macrophage function in the intestine. In response to valeric acid, a metabolite produced by intestinal microbiota, enteric serotonergic neurons express tryptophan hydroxylase-2, an enzyme involved in serotonin synthesis (137). Serotonin subsequently promotes prostaglandin E2 (PGE2) release by macrophages, which positively regulates intestinal stem cell renewal (137).

Research on neuron–macrophage interactions in the skin suggests that macrophages could also be potentially controlled by sensory neurons during intestinal inflammation. In the skin, GINIP^{+} sensory neurons support tissue healing by releasing the neuropeptide TAFA4, which acts on dermal macrophages to enhance IL-10 production after UV-induced damage (138).

3.2.4. Neuron–dendritic cell interactions. DCs are essential for mounting an adaptive immune response, as they present antigen via MHC molecules to naive T cells (139, 140). In the intestine, four different subsets of classical DCs (cDCs) are located within the lamina propria and Peyer's patches as well as in solitary intestinal lymphoid tissues (139). Upon antigen uptake, cDCs migrate via the lymph to draining mesenteric lymph nodes, where they present antigen to naive T cells (139). Another subset of DCs present in the lamina propria, the plasmacytoid DCs (pDCs), are nonmigratory but promote oral tolerance and migration of cDCs to draining lymph nodes (139).

In other tissues, DCs are regulated by VIP, CGRP, and substance P. Since these neuropeptides are also expressed by neurons in the intestine (30), they might also regulate the function of intestinal DCs. Using bone marrow–derived DCs, researchers showed that VIP promotes IL-10 expression and limits the expression of costimulatory molecules in response to LPS, suggesting that VIP induces tolerogenic DCs (141). In a coculture system of DRG neurons and bone marrow–derived DCs, neuron-derived CGRP induces transcriptional changes in DCs, resulting in an increase in sentinel functions (142). In addition, DRG neurons attract DCs via release of the chemokine CCL2 and their electrical activity induces calcium influx in DCs, leading to an increased cytokine response to immune stimuli (142). In the skin, sensory neurons release substance P in response to protease allergens, which induces migration of DCs to draining lymph nodes, where they promote the differentiation of T helper (Th) cells to Th2 cells (143).

Antigen-presenting cells (APCs), including CD103^{+} DCs and CX3CR1^{+} mononuclear phagocytes, express the muscarinic acetylcholine receptor (mAChR) and upon stimulation with acetylcholine express *Aldh1a1* and *Aldh1a2*, which encode enzymes important for the synthesis of retinoic acid (144). Retinoic acid is important for peripheral T regulatory cell (Treg) generation (145). Indeed, during DSS-induced colitis surgical division of the hepatic vagal branch led to a decline in the number of colonic Foxp3^{+} Tregs and increased intestinal inflammation (144). Further experiments revealed a neuronal circuit between the liver, brain, and intestine that limits tissue inflammation by inducing retinoic acid production by APCs, which supports intestinal Tregs (144).

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3.2.5. Neuron–T cell interactions. Tregs express the transcription factor Foxp3 and are crucial for tissue homeostasis and tolerance (146). Depending on their developmental origin, Tregs are categorized as thymus-derived Tregs (tTregs) or peripherally derived Tregs (pTregs) (145). While tTregs develop in the thymus in response to binding of self-antigen and can be identified in the intestine as Gata3$^+$ Helios$^+$ Tregs, pTregs are induced in the periphery by intestinal microbiota and are RORγt$^+$ Helios$^-$ cells (145, 146). In the small intestine, another subset of RORγt$^-$ Helios$^-$ Tregs that develop in response to food antigens has been identified (146).

Tregs are observed near CGRP$^+$ sensory neurons or nitric oxide synthase 1 (NOS1$^+$) motor neurons in the lamina propria (93). Experiments revealed that the bacterium *Clostridium ramosum* negatively regulates expression of the neuropeptide substance P (*Tac1*) in the gut (60) while also inducing Rorγ$^+$ Tregs in the colon (147). Further experiments suggested that substance P either directly or indirectly suppresses colonic Treg differentiation, since Rorγ$^+$ Treg frequencies were increased in substance P–deficient mice, and capsaicin-induced activation of intestinal TRPV1$^+$ sensory neurons reduced the frequency of Rorγ$^+$ Tregs in the colon (60). A subsequent study revealed that enteric neurons can regulate the differentiation of Tregs via release of IL-6 (93). Supernatant from enteric neurons suppressed the differentiation of conventional T cells to Foxp3$^+$ Tregs under Treg differentiating conditions in an IL-6-dependent manner, and conditional deletion of IL-6 in neurons resulted in higher Treg frequencies in the colon (93).

3.2.6. Neuron–immune cell interactions in other tissues. Although not observed in the intestine, interactions between neurons, neutrophils, and γδ T cells have been observed in other tissues, suggesting that they might also play a role in the intestine. In the skin, nociceptors secrete CGRP in response to *Streptococcus pyogenes* infection, which negatively regulates the recruitment of neutrophils and neutrophil-mediated killing of the bacterium (148). Another study showed that optogenetic activation of TRPV1$^+$ neurons in the skin induces a type 17 immune response, which reduces the bacterial and fungal load during *Staphylococcus aureus* and *Candida albicans* infection, respectively (149). In the lung, *S. aureus* induces CGRP release by TRPV1$^+$ neurons, which inhibits neutrophil recruitment and γδ T cell responses (150). In addition to these interactions, many other neuroimmune interactions in other tissues at homeostasis and in the context of infections and diseases have been described elsewhere (reviewed in 2, 17, 65, 151, 152).

3.2.7. Enteric glial cell–immune cell interactions. In addition to neurons, enteric glial cells communicate with intestinal immune cells, such as ILC3s (153), monocytes (154), and muscularis macrophages (155), and contribute to tissue repair after helminth infection (156). We do not cover this particular cross talk in this review but refer the reader to other excellent reviews on glial cell–immune cell interactions (157, 158).

3.3. Effect of Neurons on Epithelial Cells

Recent work revealed that neuronal populations also regulate intestinal diseases by communicating with epithelial cells. The intestinal epithelium consists of different epithelial cell types with separate functions, such as microfold (M) cells, which are important for antigen uptake, and mucus-producing goblet cells (159).

Upon infection with *Salmonella enterica*, mice with depleted nociceptors had significantly increased bacterial load in the ileum, Peyer's patches, and mesenteric lymph nodes and elevated bacterial dissemination to other organs, suggesting that nociceptors play a protective role in enteric bacterial infections (160). Further experiments revealed that TRPV1$^+$ nociceptors sense *S. enterica* and in response release CGRP, which negatively regulates the density of M cells in ileum Peyer's patch follicle-associated epithelia, thereby minimizing the entry points for *Salmonella*

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(160). In addition, CGRP also promotes levels of segmented filamentous bacteria, a microbial strain that offers protection against *Salmonella* infection (160).

Besides M cells, nociceptors regulate intestinal goblet cells and their production of mucus in the colon (85). scRNA-seq of ileal and colonic epithelial cells revealed that goblet cells express Ramp1, which is part of the coreceptor complex for CGRP, suggesting that goblet cells are regulated by nociceptors via CGRP (85). Nociceptors are close to goblet cells in the colon and release CGRP in response to microbiota and dietary cues (85). Moreover, a thinner mucus layer is observed both in *Calca*-deficient mice and in mice with an epithelial cell–specific Ramp1 deletion, indicating that goblet cell emptying is positively regulated by CGRP signaling (85). During DSS-induced colitis, mice with ablated nociceptors develop more severe intestinal inflammation, which is rescued by administration of CGRP, indicating an important role of this signaling pathway for epithelial barrier protection (85).

Another study showed that goblet cell function is also regulated by enteric neurons. Mice that lack IL-18 in enteric neurons show increased bacterial dissemination and succumb faster to infection by *S.* Typhimurium (161). Further experiments revealed that enteric neuron-derived IL-18 mediates its protective effect by inducing the production of antimicrobial proteins by goblet cells in the colon (161).

Goblet cells can also contribute to an immune response by creating goblet cell–associated antigen passages (GAPs), which transport antigens from the lumen to APCs in the lamina propria (162, 163). Intestinal goblet cells express mAChR4 and administration of a cholinergic agonist enhances the formation of GAPs in the small intestine (164). In contrast, blockade with a selective antagonist prevents the formation of GAPs, indicating that acetylcholine signals via mAChR4 (164). These results suggest that acetylcholine positively regulates GAP formation (164).

Several studies suggest that VIP regulates the epithelial barrier in the intestine. Coculture of the human submucosa and colonic epithelial cells revealed that activation of submucosal neurons reduces the permeability of the epithelium, presumably in a VIP-dependent manner (165). Mice lacking VIP have a dysregulated epithelial barrier (166), and administration of VIP limits epithelial permeability and body weight loss induced by *Citrobacter rodentium* infection (167). Whereas these studies suggest a protective role for VIP, another study reports that blockade of VIP signaling negatively regulates bacterial passage over human colonic epithelium ex vivo, indicating that VIP may promote epithelial permeability (168).

4. REGULATION OF NEURONS BY IMMUNE CELLS

4.1. Sensitization of Gut-Innervating Sensory Neurons by Immune Cells

During intestinal inflammation, gut-innervating sensory neurons can be sensitized by immune cells through different mechanisms, which we further describe in Sections 4.1.1–4.1.3. This sensitization leads to visceral hypersensitivity, which is often observed in patients with inflammatory intestinal diseases.

4.1.1. Intestinal inflammation and visceral pain hypersensitivity. Abdominal pain is frequently experienced by patients with IBD and IBS (43). IBS is a chronic intestinal disorder that results in visceral discomfort and pain and an altered stool pattern (43, 169). Risk factors are gastrointestinal infections, atopic diseases, psychological stress, and consumption of certain foods (169). Visceral pain develops when painful stimuli are transmitted from internal organs via afferent sensory neurons to the CNS (169). Most patients with IBS experience visceral hypersensitivity, which describes a state when either an usually innocuous stimulus is perceived as painful or a painful stimulus elicits higher sensitivity than normal in the viscera (169). In these individuals, visceral pain is long term and does not resolve after resolution of inflammation (43)

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(**Figure 4*a***). In addition to activation of usually mechanically insensitive afferents, high-threshold, distension-sensitive sensory afferents and vasculature-innervating sensory neurons become sensitized (43). Besides sensitization at nerve terminals, changes are observed in the spinal cord, where colonic afferents innervate additional areas, leading to amplified activation of dorsal horn neurons (43).

Mouse models have revealed that visceral hypersensitivity develops and accompanies intestinal inflammation. Increased visceromotor responses were measured in response to colorectal distension in mice with TNBS-induced colitis compared with control mice (170), indicating that these mice developed visceral hypersensitivity. Moreover, a higher frequency of colon-innervating DRG neurons responded to colorectal distension during TNBS-induced colitis compared with controls (171). Mice also experienced visceral pain not only during acute DSS-induced colitis but also after disease resolution (172). Notably, intestinal inflammation-induced hypersensitivity also seems to affect other distal tissue sites. During colitis, an increased withdrawal response to mechanical stimulation of the hind paws was observed in mice (170, 171). Neurons located in DRGs that innervate both the colon and the low-back skin responded stronger to skin brushes during colitis compared with controls, suggesting that visceral sensitivity can also lead to somatic hypersensitivity (171). Recently, it was reported that mice sensitized to OVA during bacterial infection develop visceral hypersensitivity when challenged orally with OVA after infection (173), suggesting that food-induced immune responses can also be a major contributor to abdominal pain. Indeed, mucosal changes in patients with IBS with likely food intolerance were immediately visible when food allergens were applied onto the mucosa of the duodenum during endoscopy (174). If the food antigen that the patient responded to was subsequently excluded from the diet, abdominal symptoms improved in most patients (174).

Recent work suggests that $TRPV1^+$ neurons promote abdominal pain. Despite similar disease severity, visceral pain was significantly reduced in mice lacking TRPV1 after resolution of DSS-induced colitis (172). Similarly, chemogenetic inhibition of $TRPV1^+$ neurons during DSS-induced colitis did not influence disease severity but reduced visceral hypersensitivity (175). In contrast, chemogenetic activation of $TRPV1^+$ neurons resulted in visceral hypersensitivity, in addition to the induction of intestinal inflammation (175).

4.1.2. Peripheral sensitization. Research over the last two decades revealed the involvement of immune cells in the peripheral sensitization of neurons in the intestine. Patients with IBS had elevated numbers of degranulating mast cells, and mast cells located close to nerve fibers in the mucosa of the colon correlated with abdominal pain (122). Supernatants of mucosal biopsies from patients with IBS contained higher levels of the mast cell mediators histamine and tryptase compared with those from healthy individuals (176–178). In vivo, increased visceral sensitivity in response to colorectal distension was observed in mice that had received colon supernatants from biopsies from patients with IBS compared with mice that received supernatants from control biopsies (178). These results suggest that mast cells promote visceral pain by sensitizing afferent sensory neurons in the intestine. Indeed, mediators released from murine mast cells and supernatant from patients with IBS activated DRG neurons in vitro (124, 176, 178). Supernatant from patients with IBS, especially patients with diarrhea-predominant IBS, increased the excitability of DRG neurons, which was diminished in protease-activated receptor 2 (PAR_2)-deficient DRGs, suggesting that sensitization of sensory neurons occurs in a protease-dependent manner (178, 179) (**Figure 4*a***). Moreover, histamine contributes to DRG neuron activation by sensitizing the TRPV1, TRPA1, and TRPV4 ion channels via histamine receptor H1 (169, 180). In contrast, resolvins, which are proresolving lipid mediators, inhibited TRPV1 sensitization in DRG neurons by histamine or substance P in vitro and negatively regulated the development of visceral hypersensitivity in vivo (181–183).

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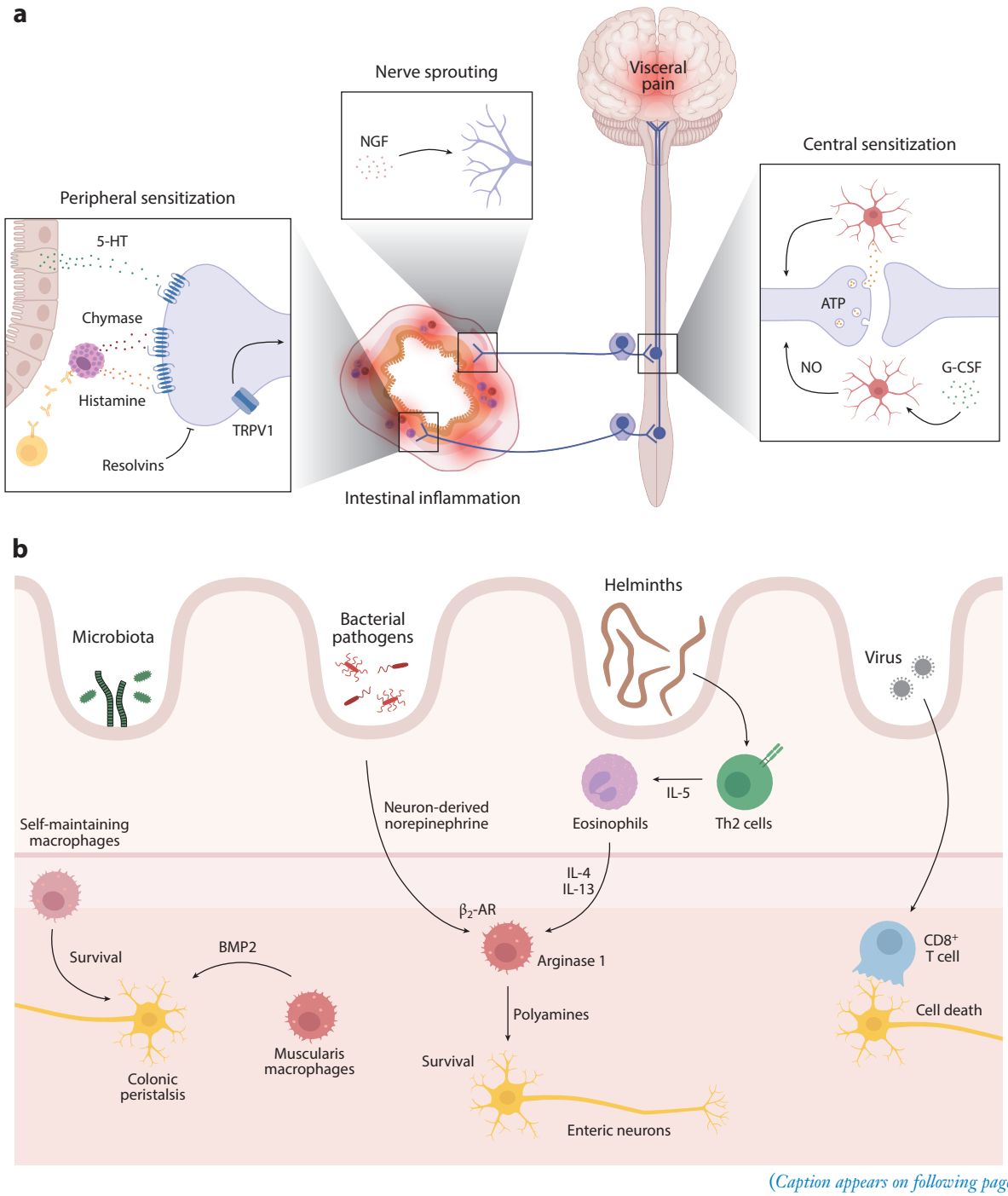

(Caption appears on following page)

Figure 4 (*Figure appears on preceding page*)

Immune cell–mediated regulation of neurons. (*a*) Visceral pain hypersensitivity develops in response to intestinal inflammation by different mechanisms, including peripheral sensitization, nerve sprouting, and central sensitization. Peripheral sensitization of sensory neurons is induced by serotonin (5-HT) released by enterochromaffin cells and chymase, histamine, and other mediators released by mast cells. Resolvins inhibit histamine-induced sensitization of transient receptor potential cation channel subfamily V member 1 (TRPV1). Another mechanism is nerve sprouting, which is associated with increased levels of nerve growth factor (NGF). Central sensitization is induced by microglia, which sensitize $TRPV1^+$ neurons upon release of ATP and activation of P2RY12 on microglia. Microglia also sensitize sensory neurons via nitric oxide (NO), which is induced by binding of granulocyte colony-stimulating factor (G-CSF) to G-CSFR on microglia. (*b*) Immune cells regulate the survival and function of neurons. Self-maintaining macrophages support the survival of enteric neurons, and muscularis macrophages promote colonic peristalsis via the secretion of bone morphogenetic protein 2 (BMP2). During bacterial enteric infection, neuron-derived norepinephrine binds to β_2-adrenergic receptor (β_2-AR) on muscularis macrophages and promotes arginase 1 expression and polyamine production to protect enteric neurons. During helminth infection, T helper type 2 (Th2)-derived IL-5 recruits eosinophils, which via IL-4 and IL-13 promote arginase 1 expression by muscularis macrophages. During viral infection, antigen-specific $CD8^+$ T cells are involved in the death of enteric neurons. Panel *a* adapted from images created with BioRender.com.

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Although not in the context of colitis, a recent study showed that during IgE-mediated anaphylaxis, the mast cell–derived protease chymase activates $TRPV1^+$ sensory neurons by binding to its receptor PAR_1 (184). As a result, warm-sensing neural circuits in the brain are activated, leading to decreased brown adipose tissue thermogenesis and hypothermia (184). In a model of food-induced visceral hypersensitivity, oral exposure to the egg antigen OVA during bacterial infection results in a localized production of OVA-specific IgE antibodies, which promoted the release of histamine from mast cells upon oral antigen challenge (173). Histamine subsequently sensitizes $TRPV1^+$ sensory neurons in a histamine receptor H1-dependent manner (173), suggesting that histamine-mediated sensitization of sensory neurons promotes abdominal pain in response to food allergens. Recent work also showed that avoidance behavior of sensitized mice to the food allergen OVA is dependent on IgE antibodies and mast cells as well as on the release of mast cell-derived leukotrienes and epithelial-derived growth and differentiation factor 15 (185, 186). These leukotrienes potentially activate vagal and/or nociceptive DRG neurons to induce oral aversion behaviors; however, a definitive role of these neurons in avoidance behavior has not been shown experimentally (185, 186).

Besides mast cells, enterochromaffin cells play a key role in sensitizing sensory neurons in the gut to drive visceral pain. Enterochromaffin cells are an epithelial cell type that is activated by microbial metabolites and chemical irritants, as well as epinephrine, norepinephrine, and dopamine (187). In response, enterochromaffin cells release 5-HT, which acts on afferent neurons via the $5\text{-}HT_3$ receptor (187). Chemogenetic activation of enterochromaffin cells promotes visceral hypersensitivity and anxiety-like behavior (188). Further experiments revealed that this phenotype can be caused by enterochromaffin cells interacting with mucosal afferents that are distension insensitive but respond to local mucosal deformation (188).

In addition to peripheral sensitization of nerve terminals, increased neuron sprouting is associated with inflammation. A higher neuron density, along with elevated expression of nerve growth factor and brain-derived neurotrophic factor, was observed in colons from patients with IBS compared with healthy individuals (189, 190), suggesting that both factors might promote nerve sprouting.

In the skin, IL-17A from microbiota-induced Th17 cells contributed to neuronal regeneration after skin injury (191) and IL-31 released from conventional type 2 DCs induced itch during wound healing by increasing the sensitivity of itch sensory neurons (192). These observations in other tissues suggest that these cytokines could also be involved in the sensitization of neurons in the intestine.

4.1.3. Central sensitization. Central sensitization describes the process in which nociceptive signals increase the sensitivity of nociceptive circuits by promoting synaptic plasticity and excitability of neurons, as well as by diminishing inhibition in the CNS (12). One study showed that granulocyte colony-stimulating factor (G-CSF) promotes the development of visceral hypersensitivity in mice recovering from DSS-induced colitis by activating spinal microglia (193) (**Figure 4*a***). Experiments suggest that G-CSF binds to the G-CSF receptor on microglia and induces the release of cathepsin S, which cleaves fractalkine (193). Subsequently, soluble fractalkine binds to CX3CR1 on microglia, which promotes nitric oxide production resulting in the hyperexcitability of DRG neurons (193). Another study revealed that activated $TRPV1^+$ neurons release ATP, which via the microglial receptor P2RY12 promotes microglia activation and neuronal sensitization (175).

4.2. Regulation of Neuronal Survival and Function

The survival and function of extrinsic and intrinsic neurons in the intestine are regulated by different immune cell types as well as by the intestinal microbiota. The pathways and mechanisms by which extrinsic and intrinsic neurons are regulated by immune cells are summarized in this section.

4.2.1. Effect of immune cells on enteric neurons. Recent work revealed an important role of different immune cell types for function and survival of enteric neurons at homeostasis and during intestinal infection and inflammation (**Figure 4*b***).

Intestinal macrophages support the survival and function of enteric neurons. Self-maintaining gut-resident macrophages are observed near myenteric neuronal ganglia and submucosal enteric neurons, and their depletion results in neuronal apoptosis in both submucosal and myenteric plexuses, leading to decreased secretion and gut motility (194). During both bacterial and helminth infections, muscularis macrophages obtain a tissue-protective phenotype and support neuronal survival (195). During infection with *S.* Typhimurium mutant *spiB*, muscularis macrophages decrease infection-induced death of enteric neurons in the intestine (134). This protective effect is dependent on β_2-adrenergic receptor signaling in muscularis macrophages and arginase 1 expression and polyamine synthesis (134). Muscularis macrophages also play an important role in preventing further neuronal loss upon reinfection. Infection with the bacterium *Yersinia pseudotuberculosis* induces loss of myenteric neurons but protects from further neuronal loss during subsequent infection with *S.* Typhimurium mutant *spiB* in a muscularis macrophage-dependent manner (195). In contrast, infection with the helminth *Strongyloides venezuelensis* does not induce neuronal loss and still prevents *spiB*-induced loss of myenteric neurons (195). Whereas this protective effect is independent of β_2-adrenergic receptor signaling (195), it requires the induction of Th2 cells and eosinophils, which via IL-4 and IL-13 promote arginase 1 expression by muscularis macrophages (195). In addition to their protective effect, muscularis macrophages modulate colonic peristalsis by producing bone morphogenetic protein 2 (BMP2), which binds to the BMP receptor on enteric neurons (132).

In contrast to muscularis macrophages, $CD8^+$ T cells are detrimental for enteric neuron survival. Inoculation of mice with the flavivirus West Nile virus results in infection of submucosal and myenteric neurons, which leads to neuronal death and decreased intestinal motility due to the infiltration of antigen-specific $CD8^+$ T cells (196). Similarly, adoptive transfer of OVA-specific $CD8^+$ T cells into transgenic mice expressing OVA in submucosal and myenteric neurons results in enteric ganglionitis and neuronal loss (197).

B cells presumably regulate intestinal neurons via the secretion of IgE. A recent study showed that most cholinergic neurons in the murine myenteric plexus express FcεRI (129). In vitro

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calcium imaging revealed that cross-linking with 2,4-dinitrophenylated bovine serum albumin (DNP-BSA) induces activation of some myenteric neurons that were preincubated with anti-DNP IgE (129).

4.2.2. Effect of microbiota on intrinsic and extrinsic neurons. Besides immune cells, the gut microbiome is important for normal intestinal motility. Mice treated with antibiotics show reduced intestinal motility (132, 198, 199), which could be rescued by administration of LPS (132). Primary enteric neurons can directly sense LPS, as stimulation of them in vitro with LPS promoted the expression of *Csf1*, a growth factor for muscularis macrophages (132). Since muscularis macrophages are important for intestinal peristalsis, the presence of microbiota promotes functional intestinal motility (132). In addition, administration of short-chain fatty acids (SCFAs) restored reduced propulsive colonic motility in germ-free mice compared with colonized mice (200). Muller et al. (201) revealed that SCFAs produced by certain bacterial consortia inhibit activation of extrinsic sympathetic neurons. Using anterograde and retrograde tracing as well as translational profiling and chemogenetic approaches, the authors identified a neuronal circuit between the intestine and brain involving vagal afferents and brainstem neurons that regulates efferent sympathetic neuron signaling and intestinal transit in response to luminal SCFAs (201). Another study showed that IPANs in the myenteric plexus are affected by the microbiota (202). Sensory neuron excitability was lower in germ-free mice than in specific pathogen-free (SPF) mice and was improved after colonization with microbiota (202). Further work has revealed that myenteric neurons in the colon express *Ahr*, which encodes the transcription factor aryl hydrocarbon receptor (AHR), in a microbiota-dependent manner (31). Conditional deletion of *Ahr* in enteric neurons resulted in reduced expression of a K^+ channel important for neuronal excitability, decreased colonic peristalsis, and prolonged intestinal transit time, suggesting that in response to microbial signals neuronal AHR promotes intestinal motility (31).

Besides a neuronal function, the structure of the ENS is dependent on the microbiome and is abnormal in early postnatal germ-free mice (203). The density of intrinsic enteric-associated neurons (iEANs) in the myenteric plexus was decreased in the duodenum and ileum but not in the colon of germ-free mice compared with SPF mice (35). Fecal transfer rescued the loss of iEANs in the ileum of germ-free mice (35). One potential mechanism by which the microbiota supports ENS function could be via serotonin, which promoted innervation of the mucosa in germ-free mice (204).

The microbiota also promotes neuronal survival and recovery at homeostasis and during infection. Viscerofugal neurons that express cocaine- and amphetamine-regulated transcript were reduced in the ileum and colon upon microbial depletion (35), indicating that the microbiota supports this neuronal subset. This neuronal subset has an important physiological role, as it regulates blood glucose levels and food intake (35). A functional microbiome is required for the recovery of enteric neurons after bacterial infection–induced death (134). Experiments revealed that bacterial enteric infection induces dysbiosis and neuronal loss, both of which are rescued after recolonization with SPF microbiota (134).

5. OUTLOOK

Research over the last 20 years has revealed an essential role for neuroimmune cross talk in the intestine both in maintaining tissue homeostasis and in regulating the outcome of intestinal inflammation. This is an exciting time for this research field, as the recent technological and genetic advances in biology will allow an in-depth characterization of neuroimmune interactions that will lead to the discovery of novel interactions and a better mechanistic understanding of them. Despite the increased interest in this field, there are still many outstanding questions and avenues that

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could be pursued, including determining how neuroimmune networks are established in the gut, at both the spatial and molecular levels, elucidating how neuroimmune interactions affect interorgan communication, and applying our knowledge of these interactions to therapeutic applications (see the Summary Points and Future Issues sections below). We believe that over the next decade studies will reveal exciting new conceptual and mechanistic insights into neuroimmune interactions with important implications for the development of novel therapies for the treatment of intestinal diseases.

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SUMMARY POINTS

1. Neuroimmune interactions are a rapidly developing research field with therapeutic implications for inflammatory diseases, such as inflammatory bowel diseases, irritable bowel syndrome (IBS), and enteric infections.
2. The intestine is innervated by intrinsic enteric neurons and extrinsic sensory, sympathetic, and parasympathetic neurons. The intrinsic enteric neurons form the enteric nervous system (ENS) and regulate intestinal motility as well as nutrient uptake and secretion, whereas extrinsic neurons transmit visceral sensory information to the central nervous system (CNS) via afferent sensory neurons and in response modulate the ENS via efferent neurons.
3. Mouse models of intestinal inflammation and infection revealed the important role of different neuronal subtypes in the development of colitis and showed that neurons release neuropeptides, neurotransmitters, and cytokines, which regulate the effector function of different immune and epithelial cell types in the intestine.
4. Intestinal inflammation promotes visceral hypersensitivity by inducing peripheral and central sensitization of gut-innervating sensory afferent neurons via inflammatory mediators.
5. Survival and function of different neuronal populations at homeostasis and during bacterial and helminth infections depend on the presence of immune cells and functional microbiota.

FUTURE ISSUES

1. Enteric neurons and colon-innervating sensory neurons have been characterized at the transcriptional level by single-cell RNA-sequencing at homeostasis. However, how are these neuronal populations changing over the lifetime and in response to inflammatory or infectious stimuli?
2. Research on neuroimmune interactions in other tissues revealed additional interactions between neurons and immune cells. Are these interactions conserved between tissues and do they also play a role in the intestine?
3. Neuropeptides and neurotransmitters have distinct effects on different immune cell types. How is the release of these distinct mediators regulated? Are they released in response to different stimuli or released at different time points or different anatomical locations?

4. How is the gut–brain axis involved in different intestinal diseases? Are there neuronal circuits connecting the intestine to organs other than the CNS that are active during intestinal inflammation?
5. How can neuroimmune interactions be targeted for therapies? Examples of a successful translation of scientific discoveries to potential therapies already exist, such as a beneficial effect of vagus nerve stimulation in patients with Crohn's disease (205, 206) and an improvement of visceral hypersensitivity and abdominal pain in patients with IBS after treatment with a mast cell stabilizer or an antagonist of histamine receptor H1 (180, 207).

DISCLOSURE STATEMENT

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